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PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Protocol Comparing Aspirin versus Low-Molecular-Weight Heparin for Blood Clot Prevention in Orthopaedic Trauma Patients

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**PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): A Randomized
Pragmatic Trial Protocol Comparing Aspirin versus Low-Molecular-Weight Heparin for
Blood Clot Prevention in Orthopaedic Trauma Patients**

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24 † PREVENT CLOT Patient Stakeholder Advisory Committee

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65 ABSTRACT

66 Introduction

67 Patients who sustain orthopaedic trauma are at an increased risk of venous thromboembolism
68 (VTE), including fatal pulmonary embolism (PE). Current guidelines recommend low-
69 molecular-weight heparin (LMWH) for VTE prophylaxis in orthopaedic trauma patients.
70 However, emerging literature in total joint arthroplasty patients suggests the potential clinical
71 benefits of VTE prophylaxis with aspirin. The primary aim of this trial is to determine if aspirin
72 is non-inferior to LMWH in preventing death due to PE within 90-days of randomization in
73 fracture patients.

75 Methods and analysis

76 PREVENT CLOT is a multi-center, randomized, pragmatic trial that aims to enroll 12,200 adult
77 patients admitted to one of 21 participating centers with an operative extremity fracture, or any
78 pelvis or acetabular fracture. Our analytical approach includes one primary estimand, the
79 difference in the treatment-specific probability of death due to PE within 90 days of
80 randomization, and seven supporting estimands to address competing risks, uncertainty in death
81 due to PE, and protocol non-adherence. Additional estimands target treatment differences with
82 respect to non-fatal PE, deep vein thrombosis, deep surgical site infections, bleeding
83 complications, and wound complications.

85 Ethics and dissemination

86 The PREVENT CLOT trial has been approved by the ethics boards of the coordinating center
87 and all participating sites. Recruitment began in April 2017 and will continue through 2021. As

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88 both study medications are currently in clinical use for VTE prophylaxis for orthopaedic trauma
89 patients, the findings of this trial can be easily adopted into clinical practice. The results of this
90 large, patient-centered pragmatic trial will help guide treatment choices to prevent VTE in
91 fracture patients.

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93 **Trial Registration:** clinicaltrials.gov Identifier: NCT02984384

For peer review only

Strengths and Limitations of this Study

- Current guidelines indicate that many fracture patients should receive medication to reduce the risk of venous thromboembolism; however, there is no consensus on the best thromboprophylaxis for this patient population.
- PREVENT CLOT was designed using patient preference research and prescribing trends in orthopaedic trauma to ensure the findings can be easily adopted into clinical practice.
- The study's 12,200 patients will be enrolled at over twenty sites in the United States and Canada and will utilize broad eligibility criteria to improve generalizability.
- Patients and providers are not blinded to the treatment allocation; however, we are monitoring site-level medication adherence and discharge prescribing to ensure similar rates on a weekly basis.

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INTRODUCTION

Traumatic Injury and the Risk of Venous Thromboembolism

Patients who sustain trauma are well known to be at an increased risk for venous thromboembolism, including fatal pulmonary embolism (PE).¹ Six million fractures are treated each year in the United States alone, and 2.3 million patients are admitted each year after orthopaedic trauma.²⁻⁴ Hip fractures are among the most common fractures and associated with a high risk of venous thromboembolism.^{5,6} Current guidelines indicate that many fracture patients should receive medication to reduce the risk of venous thromboembolism.^{7,8} Despite the frequency of these injuries and the potentially devastating impact that venous thromboembolism can have on patients' lives, the best prophylactic regimen for this patient population remains unknown.

Knowledge Gap on Venous Thromboembolism Prevention

A recent study by the Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee highlighted a knowledge gap surrounding the prevention of venous thromboembolism (VTE) in fracture patients. It concluded that there is "wide variability in practice patterns, poor scientific support for various therapeutic regimens" and guidelines are needed to "improve patient care."⁹ While healthcare practitioners clearly need guidelines on venous thromboembolism prevention in fracture patients,⁹ no large, high-quality trials upon which to base these guidelines exist.¹ Most current VTE prevention guidelines for orthopaedic trauma patients are based on extrapolated data from arthroplasty patients or elderly patients with isolated hip fractures.¹⁰ Both groups have limited generalizability to the broader orthopaedic

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3 132 trauma population, so VTE prophylaxis decisions for those patients currently lacks adequate
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5 133 evidence.
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8 134 9 10 135 **Current VTE Prophylaxis Practice Guidelines for Trauma Patients**

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12 136 The Eastern Association for the Surgery of Trauma (EAST) and the American College of Chest
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14 137 Physicians (ACCP) currently recommend low-molecular-weight heparin (LMWH) for VTE
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16 138 prophylaxis in general trauma patients.^{7,8} Therefore, many Level-1 trauma centers in the United
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18 139 States routinely use LMWH for fracture patients if they are not contraindicated for
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21 140 chemoprophylaxis.
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25 26 142 **Evidence from Total Joint Arthroplasty Suggests Effectiveness of Aspirin**

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28 143 Aspirin is an inexpensive and widely available generic antiplatelet drug. There is an emerging
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30 144 body of evidence in total joint arthroplasty patients that suggests that aspirin is as effective as
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32 145 other commonly prescribed pharmacologic agents in preventing VTE.^{11–20} While comparable
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34 146 literature in fracture patients is lacking, the growing arthroplasty evidence, combined with the
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36 147 decreased patient burden and limited complication profile associated with aspirin, has led some
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38 148 surgeons to begin prescribing aspirin for VTE prophylaxis in fracture patients.⁹
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43 44 150 **Study Objectives**

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47 151 The primary aim of PREVENT CLOT is to determine if aspirin is non-inferior to LMWH in
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49 152 preventing PE-related death in orthopaedic trauma patients within 90-days of randomization. The
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51 153 secondary objective is to compare the effects of aspirin versus LMWH in preventing non-fatal
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154 PE, DVT, infection, bleeding complication, and wound complications within 90-days of
155 randomization.

157 **METHODS AND ANALYSIS**

158 **Trial Design and Setting**

159 PREVENT CLOT is a multi-center, randomized, pragmatic trial to compare LMWH versus
160 aspirin in preventing PE-related death in fracture patients. The study will enroll patients at
161 trauma centers in the US and Canada and is co-led by the Department of Orthopaedics at the
162 University of Maryland School of Medicine and the Major Extremity Trauma and Rehabilitation
163 Consortium (METRC) Coordinating Center (MCC) at the Johns Hopkins Bloomberg School of
164 Public Health (JHSPH). The recruiting sites are listed in **Table 1**.

166 **Patient and Public Involvement**

167 The PREVENTion of Clot in Orthopaedic Trauma study (PREVENT CLOT) was designed
168 based on the clinical knowledge gap and input from patients, who identified prevention of VTE
169 and death as high priorities for their care. PREVENT CLOT investigators adhered to the 10-step
170 process for continuous patient engagement in the design and conduct of the trial, and have
171 benefited from the valuable input from a formal Patient Stakeholder Advisory Committee
172 (PSAC).²¹ The PSAC includes orthopaedic trauma patients, caregivers, clinicians, and
173 representatives from patient advocacy organizations and health insurance providers. The
174 committee meets quarterly to provide feedback on the study design, analysis, and interpretation
175 of the findings. In addition to the PSAC involvement, the study team conducted a discrete choice
176 experiment with 232 orthopaedic trauma patients to determine the relative importance of possible

177 study outcomes.²² The results of this study established our hierarchy of endpoints and non-
178 inferiority margins based on the observed acceptable trade-offs.

180 **Investigational Drug Status**

181 Both study treatments are FDA-approved medications commonly used for the indication
182 proposed in this trial. However, aspirin is considered off-label for the indication of VTE
183 prophylaxis, and an application for an Investigational New Drug (IND) exemption was approved
184 by the FDA for the proposed indications outlined in this protocol. For patients enrolled at
185 Canadian sites, the inpatient administration of aspirin and the aspirin prescribed to study
186 participants at discharge is dispensed by the treating hospital's pharmacy and complies with
187 labeling requirements outlined in the Food and Drug Regulations (C.05.011).

189 **Patient Selection**

190 Patients meeting the following eligibility criteria are recruited into PREVENT CLOT:

- 191 1) 18 years of age or older;
 - 192 2) have a planned operative or non-operative pelvis or acetabular fracture, or any operative
193 extremity fracture proximal to the metatarsals or carpals, and;
 - 194 3) and will receive a VTE prophylactic regimen per standard of care at the treating center.
- 195 Patients are excluded if they:
- 196 1) present to the hospital more than 48 hours after injury;
 - 197 2) receive more than 2 doses of LMWH or aspirin for initial VTE prophylaxis prior to consent;
 - 198 3) are on long-term anticoagulants;
 - 199 4) have been diagnosed with a VTE within the last 6 months;

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- 3 200 5) are on therapeutic, as opposed to prophylactic, anticoagulants at the time of admission;
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- 5 201 6) are diagnosed with an indication for therapeutic anticoagulants that will require therapeutic
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- 7 202 anticoagulation;
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- 10 203 7) have an allergy to aspirin or nonsteroidal anti-inflammatory drugs, or a history of heparin-
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- 12 204 induced thrombocytopenia, or other medical contraindication to anticoagulants;
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- 15 205 8) take daily aspirin with a dose greater than 81 mg for medical reasons;
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- 17 206 9) have an underlying chronic clotting disorder that requires full dose anticoagulation or is a
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- 19 207 contraindication to VTE chemoprophylaxis;
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- 21 208 10) have end-stage renal disease or impaired creatinine clearance of less than 30 ml per minute at
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- 23 209 time of screening;
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- 26 210 11) are pregnant or lactating;
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- 28 211 12) speak neither English nor Spanish;
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- 31 212 13) are incarcerated; or
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- 33 213 14) are likely to have severe problems maintaining follow-up.
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- 35 214 All patients screened for eligibility are documented as 1) eligible and included; 2) eligible and
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- 37 215 missed; and 3) excluded. In addition, all reasons that eligible patients refuse participation in the
- 38
- 39 216 trial are documented.
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44 **218 Patient Recruitment and Screening**

46 219 Once eligibility is confirmed, the research coordinator or a clinician certified to participate in this
48 220 study completes the informed consent process with the eligible study patient or a legally
50 221 authorized representative (LAR). Given the distressed condition of many eligible patients upon
52 222 admission to a participating trauma center, and the difficulty in enrolling patients immediately

upon presentation to a trauma center, the protocol allows for patients to receive up to 2 doses of the center's standard of care VTE prophylaxis regimen prior to consent and randomization. If a patient is unable to consent before the third dose of anticoagulation therapy is administered, and a LAR is not available, the patient is not eligible for study participation. Due to the acute nature of injuries experienced by the trauma patient population, some patients may have conditions or treatment plans that are unknown at the time of enrollment. Patients who are enrolled but later determined to have met an exclusionary condition that was present at the time of enrollment are considered a late ineligible patient and are removed from the study. If these participants receive study drugs, they are followed for any adverse events, but their results are not included in the study.

Study Interventions

Low-Molecular-Weight Heparin (LMWH)

Enrolled patients are prescribed a 30 mg dose of LMWH administered subcutaneously, twice daily. Adjusted dosing is permitted for obese patients and patients with renal disease, based upon each study site's existing protocols.

Aspirin

Aspirin is prescribed at an 81 mg dose, twice daily. The 81 mg dose has demonstrated effectiveness in reducing the risk of clots in the total joint arthroplasty literature.¹⁹ The twice daily frequency was selected for consistency between the 2 treatment arms and provides an equivalent daily dose with the Pulmonary Embolism Prevention trial.¹⁰

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Randomization

Patients are randomized with a 1:1 ratio with variable block sizes and stratified by clinical site using an automated structure embedded into the Research Electronic Data Capture (REDCap) system.²³ Research coordinators initiate randomization at each clinical site. Neither the patient nor the treating physician is blinded to the treatment allocation. Treatment allocation is concealed during data monitoring and analysis.

Duration and Indication for VTE Prophylaxis

No consensus exists regarding the recommended duration nor exact indication for VTE prophylaxis following a fracture, and VTE protocols currently vary between sites. Existing guidelines also vary in their recommendations, depending on the type and severity of the injury. To reflect real-world practice, the duration and indications for VTE prophylaxis are determined by the VTE prophylaxis guidelines at each center. However, the study requires all VTE doses for enrolled inpatients to be recorded in the study data. These data are monitored weekly by the MCC to ensure the duration of prophylaxis is non-differential between treatment arms at each center. Sites are notified if differential prescribing between treatment arms is observed.

Outcome Ascertainment and Adjudication

The primary study outcome is death due to PE. Data regarding patient death are collected from the medical record, including the treating physician’s determination of death and autopsy report, when available, as well as any available sources such as the Social Security Administration Death Master File, other death registries and, in some cases, phone calls. The study’s 3-person Clinical Outcome Adjudication Committee (COAC) is composed of experts not otherwise

involved in any other aspect of the study. The committee is blinded to treatment arm and receives these data with the goal of classifying the death into 1 of 5 categories: a) *Certainly PE* (e.g., an autopsy or operative note indicates cause of death), b) *More likely to be caused by PE than something else* (e.g., clinical information available indicating likely cause of death, but no autopsy or corroborating data available), c) *Equally likely to be caused by PE or something else* (e.g., patient did not die in a clinical setting, and only data available to support assignment of causality is based on the report on non-clinical family or friends), d) *More likely to be a cause other than PE* (e.g., the clinical course was highly suggestive that the cause of death was not PE), and e) *Certainly not due to PE* (e.g., the cause of death was not related to a PE). There must be agreement among at least 2 of the 3 committee members, with no more than 1 level of disagreement among members, for the cause of death category determination to be finalized.

Non-fatal PE is a key secondary outcome. The local site investigators categorize PE events, which are adjudicated centrally as one of four levels: *Massive* and *submassive* PE events are defined based on the American Heart Association recommendations²⁴; *Other clinically significant* PE events are determined when a diagnostic test was performed due to symptoms or signs concerning for PE, but the symptoms or signs do not meet the *massive* or *submassive* criteria; *Other clinically insignificant* PE events include PEs found incidentally, or as part of a test performed for screening, or for another reason that does not meet the definition of “clinically significant.” Additionally, PE events are sub-classified as being segmental or non-segmental. Similar to the adjudication of the cause of death, the categorization of PE requires two-thirds consensus from the COAC.

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Other secondary outcomes include deep vein thrombosis (DVT), deep surgical site infection (SSI), bleeding complications, and wound complications. These outcomes are not adjudicated by the COAC. DVT events can be either symptomatic or asymptomatic and require a confirmed imaging diagnosis. Deep SSI is defined based on the Centers for Disease Control and Prevention’s National Healthcare Safety Network criteria for deep or organ space infections at the fracture site²⁵ and requiring surgical treatment. The fracture-related infection (FRI) definition, an alternative to the aforementioned criteria,²⁶ was published after initiation of this study and thus is not considered when defining deep SSI. Bleeding complications are a composite endpoint previously defined in the literature that includes, 1) symptomatic bleeding into a critical area or organ, 2) bleeding causing a drop in hemoglobin level of 2 g/dL or more over a 24-hour period, or leading to transfusion of two or more units of whole blood or red cells or; 3) bleeding requiring reoperation.²⁷ Wound complications include wound drainage, hematoma, or seroma of an orthopaedic injury that requires a subsequent surgery.

Follow-Up

Participants are to be assessed at their first regularly scheduled clinical appointment that occurs 90 days after randomization. If the patient does not return to the clinic after 90 days post-randomization, they are contacted to complete the follow-up assessment by phone call or email. The 90-day assessment is performed by a research staff member at the participating center and will evaluate the occurrence of any clinical outcomes, including VTE events or complications secondary to treatment since their hospitalization. For each event identified, the participant completes a release of information form that will allow the research staff to obtain records related to the event if it occurred outside the index facility. Additionally, medical records are

carefully reviewed to assess for any complications treated at the index facility, including in the clinic, emergency department, or during a rehospitalization.

If a participant cannot be contacted and does not return for a final research visit, medical records are abstracted through the last orthopaedic clinical encounter occurring up to 6 months following injury. If no visit occurs in this interval, then the last visit is reported as the end of follow-up for that participant. At the end of the study, any participant with evidence of less than 90 days of follow-up post-randomization will be followed using alternative available sources, such as the Social Security Administration Death Master File, to capture any loss to follow up that occurred as a result of death.

Attempts will be made to obtain medical records or autopsy reports for all participants who are discovered to be deceased. If the participant dies at home, family members are asked to provide a cause of death, if known. If a patient's death is identified through a publicly available source, attempts are made to follow up with family for information on the cause of death.

Maximizing Patient Retention

Every effort will be made to retain participants in the study. The study participants will receive a \$20 honorarium in recognition of their involvement in the study after completing their 90-day post-randomization assessment.

Medication Adherence

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3 337 Accurate information on inpatient medication adherence is essential to the internal validity of the
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5 338 trial and will be closely monitored; research staff at each site complete a daily adherence report
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7 339 while a participant is an inpatient and at time of discharge. Non-adherence to the allocated
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9 340 treatment medication is defined as dose changes due to non-medical reasons, protocol crossover
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11 341 due to non-medical reasons, or patient refusal of any dosage. Medically necessary changes to the
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13 342 VTE prophylaxis are not considered non-adherence to the protocol. Some patients are not
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15 343 indicated for VTE prophylaxis at the time of discharge based on each sites' baseline practices.
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17 344 However, for the patients who are indicated for VTE prophylaxis, we also define non-adherence
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19 345 as being discharged on the non-allocated treatment for a non-medical reason. As the study is
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21 346 designed to investigate the effect of a hospital protocol for VTE prophylaxis, the study measures
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23 347 adherence during the hospitalization. Adherence after discharge from the hospital is not
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25 348 accounted for in this study.
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33 350 **Data Management and Monitoring**

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35 351 A certification process is used as the basis for training and certification of the study personnel
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37 352 involved in data collection. Ongoing data edits and audits are performed to ensure the collection
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39 353 of high quality data. The continuous and timely flow of data from the centers to the MCC is an
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41 354 essential requirement for maintaining data quality.
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46 356 Weekly enrollment reports are distributed to each center summarizing recruitment, data
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48 357 completion, and timeliness of data entry. Data queries using by the trial's REDCap²³ database are
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50 358 disseminated and expected to be resolved on a monthly basis. Site visits are conducted to
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monitor data and ensure quality data capture at least once, and more frequently depending on enrollment volume.

To prevent threats to the internal validity of the study, trial leadership obtained approval from the Data and Safety Monitoring Board (DSMB) to have real-time oversight of site-level data that is masked to the treatment allocation. The data monitoring includes the frequency of missed inpatient doses, inpatient and discharge treatment crossover rates with reasons, VTE testing rates, and study follow-up rates.

Data and Safety Monitoring Board

An independent DSMB is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review the treatment efficacy, evaluate recruitment, and assess overall data quality. The DSMB is a multidisciplinary group that will meet twice a year to review data or other issues. The DSMB may request more frequent meetings if needed. It may also request additional safety reports on a more frequent basis. The Medical Monitor prospectively reviews monthly mortality data by masked treatment arm, as well as all serious adverse events, and has the option to request a teleconference with the study's investigators based on the result of these reviews.

Estimands

Following the Addendum to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Guidance,²⁸ we define a series of estimands that are the target of estimation in this trial (**Table 2**). All estimands focus on events

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382 that occur within 90 days of randomization. Death is considered an event that preempts the
383 observation of any future events. In contrast, we consider individuals lost to follow-up as being
384 at-risk for future events. All estimands target treatment effects in a world without loss to follow-
385 up.

386
387 The primary estimand—*E1*—is the difference (aspirin minus LMWH) in the probability of being
388 observed to die due to PE (adjudication categories a and b) under assigned treatment (i.e.,
389 intention to treat[ITT]). Due to competing risks and uncertainty in cause of death, we consider 3
390 additional ITT estimands: *E2*—difference in the probability of being observed to die due to PE
391 (adjudication categories a, b and c); *E3*—difference in the probability of being observed to die
392 due to non-PE (categories d or e) related causes of death; *E4*—difference in the probability of
393 dying of any cause. To address the issue of non-adherence, we consider 4 additional estimands
394 (*E5–E8*) that mirror these 4 ITT estimands, but consider differences under assumed adherence to
395 the protocol in-hospital and at discharge.

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397 Secondary ITT estimands include: difference in the probability of being observed to have a non-
398 fatal PE, where non-fatal PE is categorized as (1) aggregated—*E9*, (2) massive—*E10*, (3) sub-
399 massive—*E11*, (4) clinically significant—*E12*, (5) clinically non-significant—*E13*, (6)
400 segmental—*E14* and (7) non-segmental—*E15*; difference in the probability of being observed to
401 have a DVT—*E16*; difference in the probability of being observed to have a deep surgical site
402 infection—*E17*; difference in the probability of being observed to have a bleeding event—*E18*;
403 and difference in the probability of being observed to have a wound complication—*E19*. We

consider 11 additional estimands (*E20–E30*) that mirror these 11 secondary ITT estimands, but consider differences under assumed adherence to the protocol in-hospital and at discharge.

Non-Inferiority Margins

The primary hypothesis is that aspirin will be non-inferior to LMWH with respect to death due to PE. The non-inferiority margin for this study was derived from discrete choice experiments in which patients indicated willingness to accept a 0.08% absolute increase in the risk of PE-related death in exchange for a specific set of benefits related to aspirin over LMWH.²² These benefits include their preference for oral medication over injectable medicine, less risk of bruising, lower out of pockets costs, and a reduction in risk of a bleeding complication. The non-inferiority margin was calculated by combining the acceptable tradeoff in medical efficacy plus the additional value-weighted benefits associated with aspirin prophylaxis. Thus, we set the non-inferiority margin at 0.36%, as the maximum increased risk of PE-related death to which the patients would be indifferent given the hypothesized benefits of aspirin over LMWH.

A secondary hypothesis is that aspirin will be non-inferior to LMWH in preventing non-fatal PE. Our non-inferiority margin of 0.87% was derived from our patient preference research.²² The margin was calculated by dividing the utility associated with oral medication compared to subcutaneous injection (utility=0.326) by the disutility associated with a 1.5% risk of non-fatal PE (disutility=0.375).

Statistical Methods

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3 426 Inference for the primary and secondary ITT estimands (*E1–E4, E9–E19*) will be based on
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5 427 cumulative incidence function estimation where individuals who are lost to follow-up prior to the
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7 428 endpoint of interest are censored.²⁹ For the estimands that consider assumed adherence to the
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9 429 protocol in-hospital and at discharge (*E5–E8*), the G-computation algorithm will be utilized.^{30,31}
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14 431 To evaluate the primary hypothesis regarding death due to PE, the upper bound of a one-sided
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16 432 95% confidence interval for the primary ITT estimand *E1* will be compared to the pre-specified
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18 433 non-inferiority margin of 0.36%. We will also use this procedure to evaluate the other mortality
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20 434 estimands (*E2–E8*). To evaluate the secondary hypothesis regarding non-fatal PE, the upper
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22 435 bound of a one-sided 95% confidence interval for the secondary ITT estimand *E9* will be
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24 436 compared to the pre-specified non-inferiority margin of 0.87%. We will also use this procedure
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26 437 to evaluate the other non-fatal PE estimands (*E10–E15 and E20–E26*).
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33 439 To evaluate treatment differences, two-sided 95% confidence intervals will also be presented for
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35 440 all estimands. There will be no multiplicity adjustments.
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40 442 **Sample Size Determination**

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42 443 The study is designed to enroll 12,200 patients. Assuming an estimated risk of death due to PE
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44 444 (categories a or b) in the LMWH arm of 0.25%,³¹ the proposed sample size provides 95% power
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46 445 to demonstrate the non-inferiority of aspirin, as compared to LMWH (*E1*). Assuming an
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48 446 estimated risk of death due to PE (categories a, b or c) in the LMWH arm of 0.445%, the
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50 447 proposed sample size provides 80% power to demonstrate the non-inferiority of aspirin, as
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52 448 compared to LMWH (*E2*). These calculations assume that death status will be known on all
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patients. Assuming a 1.5% risk of non-fatal PE (aggregated) for LMWH and a loss to follow-up of 7.5%, the proposed sample size will provide 95% power to determine non-inferiority with a 0.87% margin (*E9*).

Subgroup Analyses

Based on the credible subgroups criteria,³³ we plan to conduct subgroup analysis to compare the relative effects of the estimands based on patient age. Age will be stratified into 2 levels: under 60 years of age, and 60 years of age or older. An interaction test will be performed to assess the heterogeneity of treatment effect. We hypothesize that aspirin will be more effective in preventing death in patients 60 years of age or older than in younger patients through a different mechanism of myocardial infarction prevention—an event that is much more common in elderly patients.^{17,34}

Interim Analysis

We have 2 planned interim analyses to monitor the effect of treatment on all-cause mortality. The first interim analysis was performed when one-third of the entire patient follow-up is completed (n=4067). The second interim analysis will occur after two-thirds of the target sample size has completed their follow-up (n=8133). The primary aim of each interim analysis is to ensure that there is not a differential effect of treatment on unadjudicated death by 90 days after randomization. To preserve the type I error rate, we will utilize the O'Brien-Fleming alpha-spending approach. This approach statistically dictates stopping early for harm if either at the first interim analysis, a 99.6% confidence interval for the difference in all-cause mortality at 90

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5 472 difference in all-cause mortality at 90 days excludes zero.
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10 474 The study’s biostatistician will present the masked results of the analysis, including confidence
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12 475 intervals, to the DSMB. Following the review of each interim analysis, the DSMB will make a
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14 476 formal recommendation as to whether the trial should continue unmodified, continue with
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16 477 protocol modifications, or stop due to potential for patient harm. The study team will not have
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18 478 access to either the results of the analysis or the substance of the DSMB deliberations. After the
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20 479 first interim analysis, the DSMB recommended that the trial continue unmodified.
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26 481 **ETHICS AND DISSEMINATION**
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28 482 The study protocol, including the written consent form, was approved by the Institutional
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30 483 Review Board (IRB) at JHSPH, the Food and Drug Administration (FDA), Health Canada, and
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32 484 the local IRB at each participating center. The trial has been registered with Clinical Trials.gov
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34 485 (NCT02984384). The first patient was enrolled into the trial on April 24, 2017. We anticipate
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36 486 enrollment and follow up to be completed in June 2021.
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42 488 Orthopaedic trauma patients are known to be at an increased risk of VTE.¹ While most clinical
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44 489 guidelines currently recommend LMWH for VTE prophylaxis in the general trauma
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46 490 population,^{7,8} recent total joint arthroplasty literature suggests possible clinical benefits,^{11–20} in
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48 491 addition to the decreased administration burden of low-dose aspirin for VTE prevention.
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50 492 PREVENT CLOT aims to definitively compare LMWH with aspirin for non-inferiority in
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52 493 preventing PE and related deaths in orthopaedic trauma patients. The successful enrollment of
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the proposed 12,200 patient sample will make PREVENT CLOT the largest trial in orthopaedic trauma to date.

PREVENT CLOT is specifically designed to be pragmatic and generate clinically relevant findings. As both medications are currently being used for VTE prophylaxis,⁹ the findings of this study can be easily adopted into clinical practice. The rigorous and practical design is also responsive to patient preference and prescribing trends in orthopaedics.²² The study's 12,200 patients will be enrolled at over twenty sites in the United States and Canada and will utilize broad eligibility criteria to improve generalizability. Regular training of research staff and site monitoring has been implemented to ensure a consistently applied protocol and high data quality. The primary endpoint and secondary endpoint of PE will be adjudicated under concealed treatment allocation conditions. The trial is benefiting from the continuous engagement of patients and other stakeholders, as well as over 200 patients that responded to pre-study surveys designed to guide the trial design.²²

One limitation of this trial is that patients and providers are not blinded to the treatment allocation. Given the differential patient preferences for the routes of administration of the two medications, we are monitoring site-level medication adherence and discharge prescribing to ensure similar rates on a weekly basis. Lacking true equipoise, some providers may differentially screen for study endpoints. However, this practice is also being actively monitored. In addition, medication adherence is accounted for in the per protocol analysis.

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We will disseminate the findings of the trial through presentations at regional, national, and international scientific conferences and public forums. The primary results and secondary findings will be submitted for peer reviewed publication. In addition, we will seek widespread dissemination to the general public in collaboration with our study partners, such as the National Blood Clot Alliance and the American Trauma Society.

CONCLUSION

The optimal VTE prophylaxis for fracture patients remains controversial. Emerging evidence in arthroplasty research suggests the clinical benefits of aspirin for VTE prevention and is a preferred medication of patients.^{11–20,22} PREVENT CLOT has been designed with a patient-centered approach to inform future orthopaedic trauma practice regarding this important decisional dilemma for patients and other stakeholders.

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3 685 intervention, study outcomes, study procedures, revised the protocol critically for important
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5 686 intellectual content and approved the final version to be published. KPF made substantial
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7 687 contributions to the conception or design of the study protocol, design of the study intervention,
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42 **DISCLAIMER**

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44 703 The views, statements and opinions presented in this work are solely the responsibility of the
45
46 704 author(s) and do not necessarily represent the views of the PCORI, its Board of Governors or
47
48
49 705 Methodology Committee.
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709 CDM has received grant funding as PI from Merck and receives consulting income from
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724 competing interests.

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726 **ETHICS APPROVAL**

727 Johns Hopkins University IRB and the IRBs or Research Ethics Boards (REBs) of 19
728 participating US institutions and 2 Canadian institutions.

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730 **Table 1. Recruiting Sites for PREVENT CLOT**

| Hospital | City, State |
|---|-------------------|
| Allegheny General Hospital | Pittsburg, PA |
| Atrium Health - Carolinas Medical Center | Charlotte, NC |
| Dartmouth-Hitchcock Medical Center | Lebanon, NH |
| Harborview Medical Center | Seattle, WA |
| Indiana University – Methodist Hospital | Indianapolis, IN |
| Inova Fairfax Hospital | Falls Church, VA |
| Massachusetts General Hospital | Boston, MA |
| McGovern Medical School at UTHealth Houston | Houston, TX |
| McMaster University – Hamilton General Hospital | Hamilton, ON |
| MetroHealth Medical Center | Cleveland, OH |
| Rhode Island Hospital – Brown University | Providence, RI |
| San Antonio Military Medical Center | San Antonio, TX |
| University of Arizona | Tucson, AZ |
| University of Calgary Foothills Medical Centre | Calgary, AB |
| University of Maryland – R Adams Cowley Shock Trauma Center | Baltimore, MD |
| University of Miami – Ryder Trauma Center | Miami, FL |
| University of Mississippi Medical Center | Jackson, MS |
| University of Tennessee – RegionalOne Medical Center | Memphis, TN |
| University of Wisconsin Health University Hospital | Madison, WI |
| Vanderbilt Medical Center | Nashville, TN |
| Wake Forest University Baptist Medical Center | Winston-Salem, NC |

731

732 **Table 2. List of trial estimands with definitions and the analytical approach**

| Intention to Treat | | Per Protocol | |
|-------------------------------------|---|---------------------|---|
| Estimand | Definition | Estimand | Definition |
| Mortality | | | |
| E1 (Primary) | Difference (aspirin minus LMWH) in the probability of being observed to die due to PE (adjudication categories a and b) under assigned treatment. | E5 | Difference in the probability of being observed to die due to PE (adjudication categories a and b) under assigned treatment under assumed adherence to the protocol in-hospital and at discharge. |
| E2 | Difference in the probability of being observed to die due to PE (adjudication categories a, b and c); | E6 | Difference in the probability of being observed to die due to PE (adjudication categories a, b and c) under assumed adherence to the protocol in-hospital and at discharge; |
| E3 | Difference in the probability of being observed to die due to non-PE (categories d or e) related causes of death | E7 | Difference in the probability of being observed to die due to non-PE (categories d or e) related causes of death under assumed adherence to the protocol in-hospital and at discharge. |
| E4 | Difference in the probability of dying of any cause. | E8 | Difference in the probability of dying of any cause under assumed adherence to the protocol in-hospital and at discharge. |
| Non-Fatal Pulmonary Embolism | | | |
| E9 | Difference in the probability of being observed to have a non-fatal PE. | E20 | Difference in the probability of being observed to have a non-fatal PE under assumed adherence to the protocol in-hospital and at discharge. |
| E10 | Difference in the probability of being observed to have a massive non-fatal PE. | E21 | Difference in the probability of being observed to have a massive non-fatal PE under assumed adherence to the protocol in-hospital and at discharge. |
| E11 | Difference in the probability of being observed to have a sub-massive non-fatal PE. | E22 | Difference in the probability of being observed to have a sub-massive non-fatal PE under assumed adherence to the protocol in-hospital and at discharge. |
| E12 | Difference in the probability of being observed to have a clinically significant non-fatal PE. | E23 | Difference in the probability of being observed to have a clinically significant non-fatal PE under assumed adherence to the protocol in-hospital and at discharge. |
| E13 | Difference in the probability of being observed to have a clinically non-significant non-fatal PE. | E24 | Difference in the probability of being observed to have a clinically non-significant non-fatal PE under |

| | | | | |
|-------------------------------------|---|--|-----|--|
| | | | | assumed adherence to the protocol in-hospital and at discharge. |
| E14 | Difference in the probability of being observed to have a segmental non-fatal PE. | | E25 | Difference in the probability of being observed to have a segmental non-fatal PE under assumed adherence to the protocol in-hospital and at discharge. |
| E15 | Difference in the probability of being observed to have a non-segmental non-fatal PE. | | E26 | Difference in the probability of being observed to have a non-segmental non-fatal PE under assumed adherence to the protocol in-hospital and at discharge. |
| Deep Vein Thrombosis | | | | |
| E16 | Difference in the probability of being observed to have a deep vein thrombosis. | | E27 | Difference in the probability of being observed to have a deep vein thrombosis under assumed adherence to the protocol in-hospital and at discharge. |
| Deep Surgical Site Infection | | | | |
| E17 | Difference in the probability of being observed to have a deep surgical site infection. | | E28 | Difference in the probability of being observed to have a deep surgical site infection under assumed adherence to the protocol in-hospital and at discharge. |
| Bleeding Event | | | | |
| E18 | Difference in the probability of being observed to have a bleeding event. | | E29 | Difference in the probability of being observed to have a bleeding event under assumed adherence to the protocol in-hospital and at discharge. |
| Wound Complication | | | | |
| E19 | Difference in the probability of being observed to have a wound complication. | | E30 | Difference in the probability of being observed to have a wound complication under assumed adherence to the protocol in-hospital and at discharge. |

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BMJ Open

PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Protocol Comparing Aspirin versus Low-Molecular-Weight Heparin for Blood Clot Prevention in Orthopaedic Trauma Patients

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**PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): A Randomized
Pragmatic Trial Protocol Comparing Aspirin versus Low-Molecular-Weight Heparin for
Blood Clot Prevention in Orthopaedic Trauma Patients**

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Hospital; ¹¹ University of Texas Southwestern Medical Center; ¹² University of California,
Davis; ¹³ MetroHealth Medical Center; ¹⁴ McGovern Medical School at UTHealth Houston; ¹⁵
Patient Stakeholder Advisory Committee

24 * PREVENT CLOT Protocol Committee

25 † PREVENT CLOT Patient Stakeholder Advisory Committee

26 ‡PREVENT CLOT Adjudication Committee

27

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31

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66 ABSTRACT

67 Introduction

68 Patients who sustain orthopaedic trauma are at an increased risk of venous thromboembolism
69 (VTE), including fatal pulmonary embolism (PE). Current guidelines recommend low-
70 molecular-weight heparin (LMWH) for VTE prophylaxis in orthopaedic trauma patients.
71 However, emerging literature in total joint arthroplasty patients suggests the potential clinical
72 benefits of VTE prophylaxis with aspirin. The primary aim of this trial is to compare aspirin with
73 LMWH as a thromboprophylaxis in fracture patients.

75 Methods and Analysis

76 PREVENT CLOT is a multi-center, randomized, pragmatic trial that aims to enroll 12,200 adult
77 patients admitted to one of 21 participating centers with an operative extremity fracture, or any
78 pelvis or acetabular fracture. The primary outcome is all-cause mortality. We will evaluate non-
79 inferiority by testing whether the intention-to-treat difference in the probability of dying within
80 90 days of randomization between aspirin and LMWH is less than our non-inferiority margin of
81 0.75%. Secondary efficacy outcomes include cause-specific mortality, non-fatal PE, and deep
82 vein thrombosis. Safety outcomes include bleeding complications, wound complications, deep
83 surgical site infections.

85 Ethics and Dissemination

86 The PREVENT CLOT trial has been approved by the ethics board at the coordinating center
87 (Johns Hopkins Bloomberg School of Public Health) and all participating sites. Recruitment
88 began in April 2017 and will continue through 2021. As both study medications are currently in

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clinical use for VTE prophylaxis for orthopaedic trauma patients, the findings of this trial can be easily adopted into clinical practice. The results of this large, patient-centered pragmatic trial will help guide treatment choices to prevent VTE in fracture patients.

Trial Registration: clinicaltrials.gov Identifier: NCT02984384

For peer review only

Strengths and Limitations of this Study

- Current guidelines indicate that many fracture patients should receive medication to reduce the risk of venous thromboembolism; however, there is no consensus on the best thromboprophylaxis for this patient population.
- PREVENT CLOT was designed using patient preference research and prescribing trends in orthopaedic trauma to ensure the findings can be easily adopted into clinical practice.
- The study's 12,200 patients will be enrolled at over twenty sites in the United States and Canada and will utilize broad eligibility criteria to maximize generalizability.
- Patients and providers are not blinded to the treatment allocation; however, we will monitor and report medication adherence and discharge prescribing by treatment arm.

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INTRODUCTION

Traumatic Injury and the Risk of Venous Thromboembolism

Patients who sustain trauma are well known to be at an increased risk for venous thromboembolism, including fatal pulmonary embolism (PE).¹ Globally, over 130 million people sustain a fracture each year.² Hip fractures are among the most common fracture types and are associated with a high risk of venous thromboembolism.^{3,4} Current guidelines indicate that many fracture patients should receive medication to reduce the risk of venous thromboembolism.⁵⁻⁸ Despite the frequency of these injuries and the potentially devastating impact that venous thromboembolism can have on patients' lives, the best prophylactic regimen for this patient population remains unknown.

Knowledge Gap on Venous Thromboembolism Prevention

A recent study by the Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee highlighted a knowledge gap surrounding the prevention of venous thromboembolism (VTE) in fracture patients. It concluded that there is "wide variability in practice patterns, poor scientific support for various therapeutic regimens," and guidelines are needed to "improve patient care."⁹ While healthcare practitioners clearly need guidelines on venous thromboembolism prevention in fracture patients,⁹ no large, high-quality trials upon which to base these guidelines exist.¹ Most current VTE prevention guidelines for orthopaedic trauma patients are based on extrapolated data from arthroplasty patients or elderly patients with isolated hip fractures.¹⁰ Both groups have limited generalizability to the broader orthopaedic trauma population, so VTE prophylaxis decisions for those patients currently lack adequate evidence.

132

133 **Current VTE Prophylaxis Practice Guidelines for Trauma Patients**

134 The Eastern Association for the Surgery of Trauma (EAST) and the American College of Chest
135 Physicians (ACCP) currently recommend low-molecular-weight heparin (LMWH) for VTE
136 prophylaxis in general trauma patients.^{5,6} As such, many Level-1 trauma centers in the United
137 States and elsewhere routinely use LMWH for fracture patients if they are not contraindicated for
138 chemoprophylaxis.

139

140 **Evidence from Total Joint Arthroplasty**

141 Aspirin is an inexpensive and widely available generic antiplatelet drug. An emerging body of
142 evidence in total joint arthroplasty patients suggests that aspirin is as effective as other
143 commonly prescribed pharmacologic agents in preventing VTE.^{11–20} The results of these studies
144 have led the European Society of Anaesthesiologists to recommend aspirin for VTE prophylaxis
145 in arthroplasty and hip fracture patients.⁷ While comparable literature in fracture patients is
146 lacking, the growing arthroplasty evidence, combined with the decreased patient burden and
147 limited complication profile associated with aspirin, has led some surgeons to begin prescribing
148 aspirin for VTE prophylaxis in fracture patients.⁹

149

150 We acknowledge an emerging body of evidence that suggests direct oral anticoagulants may be
151 comparable to aspirin in preventing VTE in arthroplasty patients.^{21,22} However, there remain
152 concerns regarding an increased risk of bleeding for direct oral anticoagulants compared to
153 aspirin.^{23,24} Direct oral anticoagulants are also more costly than aspirin, making them less
154 favorable from a patient perspective.²⁵

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156 **Study Objectives**

157 The primary aim of PREVENT CLOT is to compare aspirin to LMWH for thromboprophylaxis

158 in orthopaedic trauma patients. We hypothesize that aspirin is non-inferior to LMWH in

159 preventing all-cause mortality within 90-days of randomization. The secondary objective is to

160 compare the effects of aspirin versus LMWH in preventing cause-specific mortality, non-fatal

161 PE, deep vein thrombosis (DVT), bleeding complications, wound complications, and deep

162 surgical site infections within 90-days of randomization.

163

164 **METHODS AND ANALYSIS**

165 **Trial Design and Setting**

166 PREVENT CLOT is a multi-center, randomized, pragmatic trial to compare LMWH versus

167 aspirin for thromboprophylaxis in fracture patients. The study will enroll patients at trauma

168 centers in the US and Canada and is co-led by the Department of Orthopaedics at the University

169 of Maryland School of Medicine and the Major Extremity Trauma and Rehabilitation

170 Consortium (METRC) Coordinating Center (MCC) at the Johns Hopkins Bloomberg School of

171 Public Health (JHSPH). The recruiting sites are listed in **Table 1**.

172

173 **Patient and Public Involvement**

174 The PREVENTion of Clot in Orthopaedic Trauma study (PREVENT CLOT) was designed

175 based on the clinical knowledge gap and input from patients, who identified the prevention of

176 VTE and death as high priorities for their care. PREVENT CLOT investigators adhered to the

177 10-step process for continuous patient engagement in the design and conduct of the trial, and

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3 178 have benefited from the valuable input from a formal Patient Stakeholder Advisory Committee
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5 179 (PSAC).²⁶ The PSAC includes orthopaedic trauma patients, caregivers, clinicians, and
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8 180 representatives from patient advocacy organizations and health insurance providers. The
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10 181 committee meets quarterly to provide feedback on the study design, analysis, and interpretation
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12 182 of the findings. In addition to the PSAC involvement, the study team conducted a discrete choice
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14 183 experiment with 232 orthopaedic trauma patients to determine the relative importance of possible
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16 184 study outcomes.²⁵ The results of this study established our hierarchy of endpoints and non-
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18 185 inferiority margins based on the observed acceptable trade-offs.
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23 24 187 **Investigational Drug Status**

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26 188 Both study treatments are FDA-approved medications commonly used for the indication
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28 189 proposed in this trial. However, aspirin is considered off-label for the indication of VTE
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30 190 prophylaxis, and an application for an Investigational New Drug (IND) exemption was approved
31
32 191 by the FDA for the proposed indications outlined in this protocol. For patients enrolled at
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34 192 Canadian sites, the inpatient administration of aspirin and the aspirin prescribed to study
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36 193 participants at discharge is dispensed by the treating hospital's pharmacy and complies with
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38 194 labeling requirements outlined in the Food and Drug Regulations (C.05.011).
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43 44 196 **Patient Selection**

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46 197 Patients meeting the following eligibility criteria are recruited into PREVENT CLOT:
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49 198 1) 18 years of age or older;
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51 199 2) have a planned operative or non-operative pelvis or acetabular fracture, or any operative
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53 200 extremity fracture proximal to the metatarsals or carpals, and;
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3 201 3) and will receive a VTE prophylactic regimen per standard of care at the treating center.
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8 203 Patients are excluded if they:
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10 204 1) present to the hospital more than 48 hours after injury;
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12 205 2) receive more than 2 doses of LMWH or aspirin for initial VTE prophylaxis prior to consent;
13
14 206 3) are on long-term anticoagulants;
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17 207 4) have been diagnosed with a VTE within the last 6 months;
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19 208 5) are on therapeutic, as opposed to prophylactic, anticoagulants at the time of admission;
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21 209 6) are diagnosed with an indication for therapeutic anticoagulants that will require therapeutic
22
23 anticoagulation;
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26 211 7) have an allergy to aspirin or nonsteroidal anti-inflammatory drugs, or a history of heparin-
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28 212 induced thrombocytopenia, or other medical contraindication to anticoagulants;
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31 213 8) take daily aspirin with a dose greater than 81 mg for medical reasons;
32
33 214 9) have an underlying chronic clotting disorder that requires full dose anticoagulation or is a
34
35 215 contraindication to VTE chemoprophylaxis;
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38 216 10) have end-stage renal disease or impaired creatinine clearance of less than 30 ml per minute at
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40 217 the time of screening;
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42 218 11) are pregnant or lactating;
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45 219 12) speak neither English nor Spanish;
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47 220 13) are incarcerated; or
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49 221 14) are likely to have severe problems maintaining follow-up.
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51 222 15) a diagnosis of COVID-19 at the time of fracture fixation or in the three months prior to
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53 223 fixation.
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224 All patients screened for eligibility are documented as 1) eligible and included; 2) eligible and
225 missed; and 3) excluded. In addition, all reasons that eligible patients refuse participation in the
226 trial are documented.

228 **Patient Recruitment and Screening**

229 Once eligibility is confirmed, the research coordinator or a clinician certified to participate in this
230 study completes the informed consent process with the eligible study patient or a legally
231 authorized representative (LAR). Given the distressed condition of many eligible patients upon
232 admission to a participating trauma center, and the difficulty in enrolling patients immediately
233 upon presentation to a trauma center, the protocol allows for patients to receive up to 2 doses of
234 the center's standard of care VTE prophylaxis regimen prior to consent and randomization. If a
235 patient is unable to consent before the third dose of anticoagulation therapy is administered, and
236 a LAR is not available, the patient is not eligible for study participation. Due to the acute nature
237 of injuries experienced by the trauma patient population, some patients may have conditions or
238 treatment plans that are unknown at the time of enrollment. Patients who are enrolled but later
239 determined to have met an exclusionary condition that was present at the time of enrollment will
240 be reviewed by the adjudication committee masked to treatment arm. If the adjudication
241 committee determines the patient should be classified as a late ineligible patient, they will be
242 removed from the study. If these participants receive study drugs, they are followed for any
243 adverse events, but their results are not included in the study.

245 **Study Interventions**

246 *Low-Molecular-Weight Heparin (LMWH)*

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Enrolled patients are prescribed a 30 mg dose of LMWH administered subcutaneously, twice daily. Adjusted dosing is permitted for obese patients and patients with renal disease, based upon each study site’s existing protocols.

Aspirin

Aspirin is prescribed at an 81 mg dose, twice daily. The 81 mg dose has demonstrated effectiveness in reducing the risk of clots in the total joint arthroplasty literature.¹⁹ The twice-daily frequency was selected for consistency between the 2 treatment arms and provides an equivalent daily dose with the Pulmonary Embolism Prevention trial.¹⁰

Randomization

Patients are randomized with a 1:1 ratio with variable block sizes and stratified by clinical site using an automated structure embedded into the Research Electronic Data Capture (REDCap) system.²⁷ Research coordinators initiate randomization at each clinical site. Neither the patient nor the treating physician is blinded to the treatment allocation. Treatment allocation is concealed during data monitoring and analysis.

Duration and Indication for VTE Prophylaxis

No consensus exists regarding the recommended duration nor exact indication for VTE prophylaxis following a fracture, and VTE protocols currently vary between sites. Existing guidelines also vary in their recommendations, depending on the type and severity of the injury. To reflect real-world practice, the duration and indications for VTE prophylaxis are determined by the VTE prophylaxis guidelines at each center. However, the study requires all VTE doses for

enrolled inpatients to be recorded in the study data. These data are monitored weekly by the MCC to ensure the duration of prophylaxis is non-differential between treatment arms at each center. Sites are notified if differential prescribing between treatment arms is observed.

Outcome Ascertainment and Adjudication

Primary Outcome

The primary outcome is all-cause mortality within 90 days of randomization. Data regarding patient death are collected from the medical record, including the treating physician's determination of death and autopsy report, when available, as well as any available sources such as the Limited Access Death Master File, other death registries, and, in some cases, phone calls.

The primary outcome was changed from PE-related death to all-cause mortality during the course of the trial. At the recommendation of an external peer reviewer for the protocol manuscript, the trial's steering committee determined that it was unfeasible to adjudicate death due to PE with reasonable certainty. Misclassification of the primary outcome of PE-related death would bias the results to non-inferiority. As such, the trial's steering committee decided to change the primary outcome from PE-related death to all-cause mortality. All-cause mortality was viewed as more important than PE-related death by our patient stakeholder and protocol committees and had greater scientific reliability. The Data and Safety Monitoring Board (DSMB) was not involved in these decisions due to their knowledge of treatment effect from interim analyses. The decision of the trial's steering committee to change the primary outcome and non-inferiority margin was supported by the protocol committee, patient stakeholder committee, and sponsor.

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294 *Secondary Efficacy Outcomes*

295 Secondary efficacy outcomes include cause-specific death, non-fatal PE, and DVT.

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297 Cause-specific death will be adjudicated with a specific focus on PE-related death. The study's
298 3-person adjudication committee is composed of experts not otherwise involved in any other
299 aspect of the study. The committee is blinded to the treatment arm and receives data with the
300 goal of classifying the death into 1 of 5 categories: a) *Certainly PE* (e.g., an autopsy or operative
301 note indicates cause of death), b) *More likely to be caused by PE than something else* (e.g.,
302 clinical information available indicating likely cause of death, but no autopsy or corroborating
303 data available), c) *Equally likely to be caused by PE or something else* (e.g., patient did not die in
304 a clinical setting, and only data available to support assignment of causality is based on the
305 report on non-clinical family or friends), d) *More likely to be a cause other than PE* (e.g., the
306 clinical course was highly suggestive that the cause of death was not PE), and e) *Certainly not*
307 *due to PE* (e.g., the cause of death was not related to a PE). There must be agreement among at
308 least 2 of the 3 committee members, with no more than 1 level of disagreement among members,
309 for the cause of death category determination to be finalized.

310

311 Non-fatal PE is another secondary efficacy outcome. The local site investigators categorize PE
312 events, which are adjudicated centrally by the adjudication committee as one of four levels:
313 *Massive* and *submassive* PE events are defined based on the American Heart Association
314 recommendations;²⁸ *Other clinically significant* PE events are determined when a diagnostic test
315 was performed due to symptoms or signs concerning for PE, but the symptoms or signs do not

316 meet the *massive* or *submassive* criteria; *Other clinically insignificant* PE events include PEs
317 found incidentally, or as part of a test performed for screening, or for another reason that does
318 not meet the definition of “clinically significant.” Additionally, PE events are sub-classified as
319 being segmental or non-segmental. Similar to the adjudication of the cause of death, the
320 categorization of PE requires two-thirds consensus from the adjudication committee.

321

322 The final secondary efficacy outcome is DVT. To be included as a DVT outcome, the event must
323 be symptomatic and confirmed with imaging. We will report all confirmed symptomatic DVT
324 events, and report events subclassified by proximal DVT and distal DVT.

325

326 *Secondary Safety Outcomes*

327 Safety outcomes include bleeding complications, wound complications, deep surgical site
328 infection (SSI). These outcomes are not adjudicated by the adjudication committee. Bleeding
329 complications are a composite endpoint previously defined in the literature that includes, 1)
330 symptomatic bleeding into a critical area or organ, 2) bleeding causing a drop in hemoglobin
331 level of 2 g/dL or more over a 24-hour period, or leading to transfusion of two or more units of
332 whole blood or red cells or; 3) bleeding requiring reoperation.²⁹ Wound complications include
333 wound drainage, hematoma, or seroma of an orthopaedic injury that requires a subsequent
334 surgery. Deep SSI is defined based on the Centers for Disease Control and Prevention’s National
335 Healthcare Safety Network criteria for deep or organ space infections at the fracture site and
336 requires surgical treatment.³⁰ The fracture-related infection (FRI) definition, an alternative to the
337 aforementioned criteria,³¹ was published after initiation of this study and, thus, is not considered
338 when defining deep SSI.

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340 **Follow-Up**

341 Participants are to be assessed at their first regularly scheduled clinical appointment that occurs
342 90 days after randomization. If the patient does not return to the clinic after 90 days post-
343 randomization, they are contacted to complete the follow-up assessment by a phone call or email.
344 The 90-day assessment is performed by a research staff member at the participating center and
345 will evaluate the occurrence of any clinical outcomes, including VTE events or complications
346 secondary to treatment since their hospitalization. For each event identified, the participant
347 completes a release of information form that will allow the research staff to obtain records
348 related to the event if it occurred outside the index facility. Additionally, medical records are
349 carefully reviewed to assess for any complications treated at the index facility, including in the
350 clinic, emergency department, or during a rehospitalization.

351

352 If a participant cannot be contacted and does not return for a final research visit, medical records
353 are abstracted through the last orthopaedic clinical encounter occurring up to 6 months following
354 injury. If no visit occurs in this interval, then the last visit is reported as the end of follow-up for
355 that participant. At the end of the study, any participant with less than 90 days of follow-up post-
356 randomization will be searched using other available sources, such as the Limited Access Death
357 Master File, to capture any loss to follow up that occurred as a result of death.

358

359 Attempts will be made to obtain medical records or autopsy reports for all participants who are
360 discovered to be deceased. If the participant dies at home, family members are asked to provide a

cause of death, if known. If a patient's death is identified through a publicly available source, attempts are made to follow up with family for information on the cause of death.

Maximizing Patient Retention

Every effort will be made to retain participants in the study. The study participants will receive a \$20 honorarium in recognition of their involvement in the study after completing their 90-day post-randomization assessment.

Medication Adherence

Accurate information on inpatient medication adherence and the medication prescribed at discharge is essential to the internal validity of the trial and will be closely monitored; research staff at each site complete a daily adherence report while a participant is an inpatient and at time of discharge. To be classified as protocol adherent, patients must meet the following definition:

- 1) if the patient is prescribed thromboprophylaxis at discharge, the patient must be discharged on the allocated study medication; 2) the patient must have been adherent for at least 80% of their in-hospital study medication doses. Dosage changes due to non-medical reasons, protocol crossovers due to non-medical reasons, and patient refusal to continue medication will be considered non-adherence. Medically necessary changes to the VTE prophylaxis are not considered non-adherence to the protocol. As the study is designed to investigate the effect of a hospital protocol for VTE prophylaxis, the study measures adherence during the hospitalization and at discharge. Adherence after discharge from the hospital is not accounted for in this study.

Data Management and Monitoring

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A certification process is used as the basis for training and certification of the study personnel involved in data collection. Ongoing data edits and audits are performed to ensure the collection of high quality data. The continuous and timely flow of data from the centers to the MCC is an essential requirement for maintaining data quality.

Weekly enrollment reports are distributed to each center summarizing recruitment, data completion, and timeliness of data entry. Data queries using the trial’s REDCap database are disseminated and expected to be resolved on a monthly basis.²⁷ Site visits are conducted to monitor data and ensure quality data capture at least once, and more frequently depending on enrollment volume.

To prevent threats to the internal validity of the study, trial leadership obtained approval from the DSMB to have real-time oversight of site-level data that is masked to the treatment allocation. The data monitoring includes the frequency of missed inpatient doses, inpatient and discharge treatment crossover rates with reasons, VTE testing rates, and study follow-up rates.

Data and Safety Monitoring Board

An independent DSMB is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety, evaluate recruitment, and assess overall data quality. The DSMB is a multidisciplinary group that will meet twice a year to review data or other issues. The DSMB may request more frequent meetings if needed. It may also request additional safety reports on a more frequent basis. The Medical Monitor prospectively reviews monthly mortality

data by masked treatment arm, as well as all serious adverse events, and has the option to request a teleconference with the study's investigators based on the result of these reviews.

Estimands

Following the Addendum to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Guidance,³² we define a series of estimands that are the target of estimation in this trial (**Table 2**). All estimands focus on events that occur within 90 days of randomization. We will treat all-cause death as a competing risk for non-fatal events and cause-specific death as a competing risk for other causes of death. The primary analysis will use an intention to treat approach, as the pragmatic design aims to determine non-inferiority at the policy level. A secondary analysis will estimate the effect among those adherent to the treatment protocol.

Non-Inferiority Margins

The primary hypothesis is that aspirin will be non-inferior to LMWH with respect to all-cause mortality. The trial's non-inferiority margin was derived from patient preference research and a survey of clinical experts that indicated a willingness to accept a 0.75% absolute increase in the risk of death in exchange for a specific set of benefits related to aspirin over LMWH.²⁵ These benefits include preferences for oral medication over injectable medicine, less risk of bruising, and lower out of pockets costs.

Statistical Methods

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Inference for the primary estimand (E1) will be calculated using treatment-specific Kaplan-Meier estimators. Secondary estimands (E2–E9) will be based on cumulative incidence function estimation where individuals who are lost to follow-up prior to the endpoint of interest are censored.³³ A secondary analysis will estimate the estimands using a per-protocol analysis. The per-protocol estimands will only include the subset of patients classified as protocol adherent. To the extent possible, we will adjust for baseline differences between the per-protocol treatment groups. Missing baseline covariates will be imputed using multiple imputation.

To evaluate the primary hypothesis regarding all-cause mortality, we will compare the upper bound of a two-sided 96.2% confidence interval for the primary intention to treat estimand to the pre-specified non-inferiority margin of 0.75%. If non-inferiority is established, we will test the primary estimand for superiority. For all other estimands, we will report point estimates with two-sided 95% confidence intervals. We will not perform hypothesis testing for the secondary estimands.

Subgroup Analyses

Based on the credible subgroups criteria,³⁴ we plan to conduct subgroup analysis to compare the effects of the primary estimand based on patient age. Age will be stratified into 2 levels: under 60 years of age, and 60 years of age or older. An interaction test will be performed to assess the heterogeneity of the treatment effect. We hypothesize that aspirin will be more effective in preventing death in patients 60 years of age or older than in patients under 60 years of age through a different mechanism of myocardial infarction prevention—an event that is much more common in patients 60 years of age or older.^{17,35}

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452 Sample Size Determination

453 The study is designed to enroll 12,200 patients. Assuming an estimated risk of death in the
454 LMWH arm of 1.0%,^{36,37} the proposed sample size provides 95% power to demonstrate the non-
455 inferiority of aspirin with a non-inferiority margin of 0.75% at the upper bound of a two-sided
456 96.2% confidence interval, as compared to LMWH. These calculations account for two interim
457 analysis and allows for an attrition rate up to 7.5%.

458

459 Interim Analysis

460 We have 2 planned interim analyses to monitor trial safety based on all-cause mortality. The first
461 and second interim analyses were performed when approximately one-third (n= 4000) and two-
462 thirds (n=8000) of patients were expected to complete 90 days of follow-up. The primary aim of
463 each interim analysis was to ensure that there is not a differential effect of treatment on death by
464 90 days after randomization. To preserve the type I error rate, we will utilize the alpha-spending
465 approach. This approach statistically dictates stopping early for harm if either at the first interim
466 analysis, a 99.6% confidence interval for the difference in all-cause mortality at 90 days excludes
467 zero, or at the second interim analysis, a 98.8% confidence interval for the difference in all-cause
468 mortality at 90 days excludes zero.

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470 The study's biostatistician presented the masked results of the analysis, including confidence
471 intervals, to the DSMB. Following the review of each interim analysis, the DSMB made a formal
472 recommendation to continue the trial. The study team did not have access to either the results of

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the analysis or the substance of the DSMB deliberations. After both interim analyses, the DSMB recommended that the trial continue unmodified.

ETHICS AND DISSEMINATION

The study protocol, including the written consent form (an example of the consent form is included as a *Supplementary File*), was approved by the Institutional Review Board (IRB) at JHSPH, the Food and Drug Administration (FDA), Health Canada, and the local IRB at each participating center. The trial has been registered with Clinical Trials.gov (NCT02984384). The first patient was enrolled into the trial on April 24, 2017. We anticipate enrollment and follow up to be completed by the end of 2021.

Orthopaedic trauma patients are known to be at an increased risk of VTE.¹ While most clinical guidelines currently recommend LMWH for VTE prophylaxis in the general trauma population,^{5,6} recent total joint arthroplasty literature suggests possible clinical benefits,^{7,11–20} in addition to the decreased administration burden of low-dose aspirin for VTE prevention. PREVENT CLOT aims to definitively compare LMWH with aspirin for non-inferiority as a thromboprophylaxis in orthopaedic trauma patients. The successful enrollment of the proposed 12,200 patient sample will make PREVENT CLOT the largest trial in orthopaedic trauma to date.

PREVENT CLOT is specifically designed to be pragmatic and generate clinically relevant findings. As both medications are currently being used for VTE prophylaxis,⁹ the findings of this study can be easily adopted into clinical practice. The rigorous and practical design is also

responsive to patient preference and prescribing trends in orthopaedics.²⁵ The study's 12,200 patients will be enrolled at over twenty sites in the United States and Canada and will utilize broad eligibility criteria to improve generalizability. Regular training of research staff and site monitoring has been implemented to ensure a consistently applied protocol and high data quality. The secondary endpoints of cause-specific death and non-fatal PE will be adjudicated under concealed treatment allocation conditions. The trial is benefiting from the continuous engagement of patients and other stakeholders, as well as over 200 patients that responded to pre-study surveys designed to guide the trial design.²⁵

The trial has several limitations. The patients and providers are not blinded to the treatment allocation. Given the differential patient preferences for the routes of administration of the two medications, we are monitoring site-level medication adherence and discharge prescribing to ensure similar rates on a weekly basis. Lacking true equipoise, some providers may differentially screen for study endpoints. However, this practice is also being actively monitored. In addition, medication adherence is accounted for in the per-protocol analysis.

We will disseminate the findings of the trial through presentations at regional, national, and international scientific conferences and public forums. The primary results and secondary findings will be submitted for peer reviewed publication. In addition, we will seek widespread dissemination to the general public in collaboration with our study partners, such as the National Blood Clot Alliance and the American Trauma Society.

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518 The optimal VTE prophylaxis for fracture patients remains controversial. Emerging evidence in
519 arthroplasty research suggests the clinical benefits of aspirin for VTE prevention and is a
520 preferred medication of patients.^{11–20,25} PREVENT CLOT has been designed with a patient-
521 centered approach to inform future orthopaedic trauma practice regarding this important
522 decisional dilemma for patients and other stakeholders.

For peer review only

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689
690 **AUTHOR’S CONTRIBUTIONS**

691 RVO, DMS, GPS, TT, BEH, ARC, TTM, CDM, STW, RF, ERH, DM, and RCC each made
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693 intervention, study outcomes, study procedures, revised the protocol critically for important
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696 study outcomes, study procedures, wrote the first draft of the protocol. NNO made substantial
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702 All authors approved the final version to be published.

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712 DISCLAIMER

713 The views, statements and opinions presented in this work are solely the responsibility of the
714 author(s) and do not necessarily represent the views of the PCORI, its Board of Governors or
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718 COMPETING INTERESTS

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ETHICS APPROVAL

Johns Hopkins University IRB and the IRBs or Research Ethics Boards (REBs) of 19
participating US institutions and 2 Canadian institutions.

740 **Table 1. Recruiting Sites for PREVENT CLOT**

| Hospital | City, State |
|---|--------------------|
| Allegheny General Hospital | Pittsburg, PA |
| Atrium Health - Carolinas Medical Center | Charlotte, NC |
| Dartmouth-Hitchcock Medical Center | Lebanon, NH |
| Harborview Medical Center | Seattle, WA |
| Indiana University – Methodist Hospital | Indianapolis, IN |
| Inova Fairfax Hospital | Falls Church, VA |
| Massachusetts General Hospital | Boston, MA |
| McGovern Medical School at UTHealth Houston | Houston, TX |
| McMaster University – Hamilton General Hospital | Hamilton, ON |
| MetroHealth Medical Center | Cleveland, OH |
| Rhode Island Hospital – Brown University | Providence, RI |
| San Antonio Military Medical Center | San Antonio, TX |
| University of Arizona | Tucson, AZ |
| University of Calgary Foothills Medical Centre | Calgary, AB |
| University of Maryland – R Adams Cowley Shock Trauma Center | Baltimore, MD |
| University of Miami – Ryder Trauma Center | Miami, FL |
| University of Mississippi Medical Center | Jackson, MS |
| University of Tennessee – RegionalOne Medical Center | Memphis, TN |
| University of Wisconsin Health University Hospital | Madison, WI |
| Vanderbilt Medical Center | Nashville, TN |
| Wake Forest University Baptist Medical Center | Winston-Salem, NC |

Table 2. List of trial estimands with definitions

| Estimand | Definition |
|-------------------------------------|--|
| <i>Primary Outcome</i> | |
| E1 | Difference (aspirin minus LMWH) in the probability of dying of any cause. |
| <i>Secondary Efficacy Outcomes</i> | |
| <i>Cause-Specific Mortality</i> | |
| E2 | Difference in the probability of being observed to die due to PE (adjudication categories a and b) under assigned treatment. |
| E3 | Difference in the probability of being observed to die due to PE (adjudication categories a, b and c); |
| E4 | Difference in the probability of being observed to die due to non-PE (categories d or e) related causes of death |
| <i>Pulmonary Embolism</i> | |
| E5.1 | Difference in the probability of being observed to have a non-fatal PE. |
| E5.2 | Difference in the probability of being observed to have a massive non-fatal PE. |
| E5.3 | Difference in the probability of being observed to have a sub-massive non-fatal PE. |
| E5.4 | Difference in the probability of being observed to have a clinically significant non-fatal PE. |
| E5.5 | Difference in the probability of being observed to have a clinically non-significant non-fatal PE. |
| E5.6 | Difference in the probability of being observed to have a segmental non-fatal PE. |
| E5.7 | Difference in the probability of being observed to have a non-segmental non-fatal PE. |
| <i>Deep Vein Thrombosis</i> | |
| E6.1 | Difference in the probability of being observed to have symptomatic deep vein thrombosis. |
| E6.2 | Difference in the probability of being observed to have proximal deep vein thrombosis. |
| E6.3 | Difference in the probability of being observed to have distal deep vein thrombosis. |
| <i>Secondary Safety Outcomes</i> | |
| <i>Bleeding Event</i> | |
| E7 | Difference in the probability of being observed to have a bleeding event. |
| <i>Wound Complication</i> | |
| E8 | Difference in the probability of being observed to have a wound complication. |
| <i>Deep Surgical Site Infection</i> | |
| E9 | Difference in the probability of being observed to have a deep surgical site infection. |

745 **Supplementary Files**

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747 S1. Example of a patient consent form.

For peer review only

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ATTACHMENT A: CONSENT FORM
JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH
INFORMED CONSENT DOCUMENT

Patient Consent Form

Study Title: PREVENTion of Clot in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients

Principal Investigator: Robert O’Toole, MD (Clinical PI) and Renan Castillo, PhD (Research PI)
IRB No.:
PI Version Date: Version 5; 9/25/2020

You are being asked to volunteer to be a part of a research study. Please read this form carefully before you sign it. This consent form explains the research study and your part in the study. It is up to you whether or not you want to be in this study. If you decide not to join the study, there will be no impact on your medical care. If you decide to join the study, you may quit at any time. Please ask the study doctor or staff to explain any words or procedures that are not clear. Please ask as many questions as you like. All of your questions should be answered to your satisfaction before you sign this form.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

People who have surgery or trauma are at risk for blood clots. The purpose of this research study is to help figure out the best way to prevent blood clots after trauma. Blood clots can be very serious and can lead to death. Right now, doctors use two different medicines to prevent blood clots, but they don’t know which one is better. One of these medicines to prevent blood clots is called low molecular weight heparin, or Lovenox. The other medicine doctors sometimes use is aspirin. This study is being done to find out whether low molecular weight heparin (Lovenox/Enoxaparin) or aspirin is better in preventing life threatening blot clots in trauma patients. Patients who join this study will get either the low molecular weight heparin (Lovenox/Enoxaparin) or aspirin to prevent blood clots. The low molecular weight heparin (Lovenox/Enoxaparin) is given by injection (shot). The aspirin is a pill taken by mouth or given through a feeding tube. Patients in this study will start their medicine in the hospital and then take the same medicine once they go home. We will then compare the medicines to see which one was better at preventing blood clots.

A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients Version 5.0 9/25/2020 1

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The PREVENT CLOT Study is funded by the Patient-Centered Outcomes Research Institute (PCORI). The study is being done in more than 20 major trauma centers across the United States and Canada, including military centers that are taking care of service members who were injured in the line of duty.

2. WHY AM I BEING ASKED TO PARTICIPATE?

You are being asked to join this study because you are at least 18 years old and have had a traumatic orthopaedic injury(ies) which puts you at increased risk of blood clots. Your doctor believes you need to take blood clot prevention medicine. People around the country who need to start blood clot prevention medicine after trauma are being asked to take part in this study. You are one of over 12,000 patients expected to join the PREVENT CLOT study.

3. HOW LONG WILL THE STUDY LAST?

If you agree to take part in this study, we will follow up with you for up to three months after admission to the hospital for your traumatic injury. If the research team is unable to get in contact with you or someone you know, a member of the research team will review your medical record in order to record any information that is usually collected during the follow up visit.

4. HOW DOES THE STUDY WORK?

If you agree to join the PREVENT CLOT Study you will be assigned randomly, or by chance, (like flipping a coin) to one of the two treatments being studied:

- Treatment A: Low molecular weight heparin (Lovenox/Enoxaparin) medicine given two times a day as a shot or injection.
- Treatment B: Aspirin medicine given two times a day in pill form by mouth or feeding tube.

You will get *one* of these medicines as part of your normal treatment for your injuries. If you were not in the study, your doctor would make the choice about which of these medicines you would receive. In this study, you have an equal chance of getting either one of the treatments and the treatment you receive will be decided by chance and not by your treating physician. Deciding randomly who gets the low molecular weight heparin (Lovenox/Enoxaparin) and who gets the aspirin is the best way to find out which medicine is better at preventing blood clots. Right now, we don't know which medicine is better at preventing clots for people with traumatic injuries.

If you join the study, you will begin receiving medicine as soon as your doctors want you to start taking medicine to prevent blood clots. Usually this is immediately after you are enrolled. When you are discharged from the hospital you will continue taking the same medicine you were assigned for however long your doctor wants. Being in the study does not affect how long you take your medicine; your doctor makes that decision based on the types of injuries you have and

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any other medical conditions you may have. For example, for some types of injuries doctors may give the medicine for several weeks after patients leave the hospital. For other types of injuries people may need to take the medicine for several months.

Following discharge we would like to contact you every week. At the end of this form you will be able to let us know if you prefer to be contacted weekly by telephone call, text message or email, or not at all. These calls will come from a computerized system at the study coordinating center at Johns Hopkins. We will ask you how many times you took your medication that week and the interview will last for about 3 minutes. You will be able to let us know the best way to contact you at the end of this form. If you do not reply to these messages, a member of the study team may call you to see how things are going and if you no longer want to receive weekly contact you will be able to let the study team know at the end of the call, text or email. If you prefer you may complete a post card with a calendar telling us what days you took your medicine.

You will come back for your normal follow up clinic visit with your surgeon approximately 3 months after your hospitalization. When you come for the 3 month follow up, we will ask you to do a 15-30 minute interview for this study. You will be asked questions about how your recovery is going, your overall satisfaction with the medicine you took to prevent blood clots, and overall how much money you spent on the medicine you took to prevent blood clots. If you are not able to come back, we may contact you by telephone or email to do these interviews.

While you are in the study, a member of the research team at your medical center will also review your medical record to see if you had any blood clots or other visits related to your injury. Your medical record will also be reviewed to see if you were tested for COVID-19 and record the results of your test (positive or negative). Your COVID-19 results, along with all other information collected for the purposes of this study, will be kept confidential.

Option A: If you do not complete any study visits and the study team is unable to speak with you or someone else who knows how things are going with you, the study team will send information about you, which may include your name, data of birth, and social security number, to the study team at Johns Hopkins, where they will enter the information into a large administrative database called the Limited Access Death Master File, which maintains records of all deaths that have been recorded in the social security system. This may enable the team to determine why you cannot be contacted. Your data will not be recorded or maintained by the study team once the search is complete.

Option B: If you do not complete any study visits and the study team is unable to speak with you or someone else who knows how things are going with you, the study team will enter information about you, which may include your name, data of birth, and social security number, into a large administrative database called the Limited Access Death Master File, which maintains records of all deaths that have been recorded in the social security system. This may enable the team to determine why you cannot be contacted. Your data will not be recorded or maintained by the study team once the search is complete.

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5. WHAT ARE THE POTENTIAL RISKS OR DISCOMFORTS?

This study is comparing two widely used medicines. Each of these medicines has benefits; each also has some risks.

The risks of taking either medication are as follows:

- **Risks of Treatment A (Low molecular weight heparin (Lovenox/enoxaparin)):** nausea; diarrhea, injection site irritation, bruising, pain or possible infection; allergic reaction ranging from hives and itching to difficulty breathing or throat swelling; Heparin Induced Thrombocytopenia which results in a reduced number of platelets and impaired ability to form clots; bleeding complications which could require transfusion or operation and kidney damage.
- **Risk of Treatment B (Aspirin):** Risk of inflammation or ulceration of the stomach, allergic reaction (ranging from hives and itching to difficulty breathing or throat swelling), ringing of the ears, and worsening asthma. Increased risk of bleeding and of kidney damage. Potential risk of Reyes syndrome in younger participants during influenza season. Symptoms of Reyes syndrome include: fever, lack of energy or interest in things, sleepiness, changes in personality, vomiting or diarrhea.

The following symptoms are uncommon but extremely serious risks that can be associated with these medication. If you experience any of the following risks you should immediately go to the nearest emergency room:

Signs of bleeding, including vomiting blood or vomit that looks like coffee grounds; coughing up blood; blood in the urine, black, red or tarry stools, bleeding from the gums, abnormal vaginal bleeding; bruising without a reason or that get bigger; or any severe or persistent bleeding), Severe dizziness, Fainting, Fall or head injury, Confusion, Severe headache, Burning or numbness feeling or loss of strength. Signs of significant allergic reaction, including (wheezing, chest tightness, fever, itching, tight cough; change in skin color; seizures or swelling of face, lips, tongue or throat.)

If any of those happens, we would appreciate your also letting the study team know as well, once you are stable and feel better.

6. WHAT ARE THE POTENTIAL BENEFITS?

Patients after trauma need a medicine to prevent blood clots. You will get a medicine that will prevent blood clots in this study. Beyond that, you will not benefit from being in this study, but your being in this study will help us learn, for patients in the future with trauma, which of the two medicines works best for preventing blood clots.

7. DO I GET ANY PAYMENT FOR BEING IN THE STUDY?

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You will receive \$20 in recognition of your time and effort after completing the 3 month visit in person, over the phone or by email.

8. ARE THERE ANY COSTS INVOLVED IN BEING IN THE STUDY?

All charges associated with your treatment will be billed to you or your insurance. There are no increased costs for taking part in this research study. The costs of your usual medical care are not covered by the study but will be billed to your insurance or to you, just as usual.

9. WILL MY INFORMATION BE KEPT PRIVATE?

The information we collect from you will be kept private to the best of our ability. We will be collecting information about any treatment you received in the hospital and after you leave the hospital, and asking you questions about your recovery. Your name, birth date, medical record number and any other information that could identify you will not be recorded on these data collection forms. Instead, we will label your forms with a unique study number. The information we collect on a weekly basis through the phone calls, texts, or emails, will be stored in a separate database. We will link the information between these two databases using only the study number. The link between your name and your study number will be kept confidential to the greatest extent provided by law. The information collected for the study will be stored in a password protected, HIPAA compliant computer database that only authorized members of our research team can use. When we report the results of the study, we will combine the information about you with similar information about hundreds of other people, and without names. That way, your individual information will not be identifiable.

All study records will be considered confidential, and your name will not be used in reports or publications.

10. WILL YOU SHARE MY INFORMATION WITH OTHERS?

Your name and the phone number and/or email you provide will be shared with investigators at the data coordinating center at the Johns Hopkins Bloomberg School of Public Health if you choose to participate in this part of the study. This information will be stored separately from all study data, and will be used only for reaching out to you to see how things are going with taking your medicine every week. After your participation in the study is complete, we will destroy this information.

We will use the information we collect from you only for the purposes of this study. Large groups of data from the study may be published. You will never be identified by name. People from each participating research institution may look at sections of your medical and research records related to the study. This includes people designated by The Johns Hopkins Bloomberg School of Public Health who are overseeing this study. Everyone using study information will

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work to keep your personal information confidential. Your personal information will not be given out unless required by law.

The Patient-Centered Outcomes Research Institute (PCORI) is the group funding this study. Our funder and the ethics committee (IRB) are also allowed to look at research records if they believe it will help protect the people in the study.

11. WHAT ARE MY ALTERNATIVES TO PARTICIPATION?

Your alternative is to not take part. If you choose not to take part, your healthcare will not be affected and you will still receive blood clot prevention medicine. Your doctor will make the choice of what medicine to give you.

You may also participate in the study and choose not to participate in the weekly calls. This will not affect any other part of your participation in the study.

12. WHAT HAPPENS IF I LEAVE THE STUDY EARLY?

Your participation in this study is completely voluntary. You have the right to withdraw from the research study at any time without penalty. Your decision will not affect the medical care you receive. If you decide to stop participating, you should notify the study doctor or the research coordinator at your center.

You may choose to stop participating in the weekly contact at any time, and it will not affect your participation in the overall study.

Your participation in this research study could be ended by the researchers, either because the study is ending early or for other reasons.

13. WHAT HAPPENS IF I AM INJURED OR BECOME ILL BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or become ill because you were part of this study, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of care, just as you would be billed for any other medical care. If you have any costs that are not covered by insurance, they are your responsibility.

You do not give up any of your legal rights by signing this form. You can seek legal compensation for any injury that may occur to you during the study as a result of an error by a member of the research staff or others.

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14. WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

- <<insert name>>, the study coordinator at your hospital has discussed this information with you and offered to answer any questions you may have. If you have further questions or get sick or injured as a result of being in this study, you can contact << insert him/her>> at <<telephone number>>. You may also call the Director of the Study at your hospital, <<insert name>>, at <<telephone number>>.
- If you have further questions about your rights as a study participant you can call or contact the Johns Hopkins Bloomberg School of Public Health IRB Office. The Johns Hopkins Bloomberg School of Public Health is serving as the overall coordinating center for this study that is being conducted in hospitals around the country. Contact the Johns Hopkins IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

Address: Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street, Suite E1100
Baltimore, MD 21205
Telephone: 410-955-3193
Toll Free: 1-888-262-3242
Fax: 410-502-0584
E-mail: irboffice@jhsph.edu

Please let us know what way you would like to be contacted and which way your prefer.

| Which methods may we use to contact you? (check all that apply): | What is your preferred communication method? |
|---|---|
| <input type="checkbox"/> Phone call | <input type="checkbox"/> |
| <input type="checkbox"/> Text message | <input type="checkbox"/> |
| <input type="checkbox"/> Email | <input type="checkbox"/> |
| <input type="checkbox"/> Mail | <input type="checkbox"/> |
| <input type="checkbox"/> I do not want to be contacted weekly | |

What does your signature (or thumbprint/mark) on this consent form mean?

Your signature (or thumbprint/mark) on this form means:

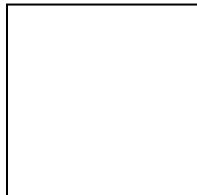
- You have been informed about this study’s purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

The PREVENT CLOT study protocol is the confidential intellectual property of the PREVENT CLOT Principal Investigators, Steering Committee, and the University of Maryland Baltimore and METRC and cannot be used in any form without the expressed permission of the Principal Investigators.

Print name of Adult Participant Signature of Adult Participant Date

Print name of Legally Authorized Representative (LAR) Signature of LAR Date

Relationship of LAR to Participant



Ask the participant to mark a “left thumb impression” in this box if the participant (or participant’s parent) is unable to provide a signature above.

Print name of Person Obtaining Consent Signature of Person Obtaining Consent Date

Give one copy to the participant and keep one copy in study records

A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients Version 5.0 9/25/2020 8



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|-----------------------------------|---------|---|
| Administrative information | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – Pg 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry – Pg. 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set -- NA |
| Protocol version | 3 | Date and version identifier – Pg 2. |
| Funding | 4 | Sources and types of financial, material, and other support – Pg 33 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors Pg 1, 32, 33 |
| | 5b | Name and contact information for the trial sponsor – Pg. 33 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities. -- Pg 33. |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – Pg 9, 13-14, 17-18 |
| Introduction | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – Pg 7-9 |
| | 6b | Explanation for choice of comparators – Pg 8 |
| Objectives | 7 | Specific objectives or hypotheses -- Pg 8 |

| | | |
|--------------|---|--|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) – Pg 8 |
|--------------|---|--|

Methods: Participants, interventions, and outcomes

| | | |
|----------------------|-----|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained – Pg. 9 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) – Pg 10-11 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – Pg 12 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) – Pg 13 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Pg 16-17 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial – Pg 11-12 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended – Pg 13-15 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) – Pg 16-17 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations – Pg 21-22 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size – Pg 16 |

Methods: Assignment of interventions (for controlled trials)

Allocation:

| | | |
|---|-----|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – Pg 13 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned – Pg 13 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – Pg 13 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how – Pg 13. |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – Pg 13 |
| Methods: Data collection, management, and analysis | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – Pg 13-15 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – Pg 16 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – Pg 17-18 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol -- Pg 21-22 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) -- Pg 22 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – Pg 18-20 |

Methods: Monitoring

| | | |
|-----------------|-----|--|
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed -- Pg 18 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial – Pg 22-23 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct – Pg 18 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – Pg 17-18 |

Ethics and dissemination

| | | |
|-------------------------------|-----|--|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – Pg 23 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – Pg 18 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – Pg 11-12 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – N/A |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – Pg 17-18 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site – Pg 34 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – Pg 17-18 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation - NA |

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| 1 | | | |
| 2 | Dissemination | 31a | Plans for investigators and sponsor to communicate trial results to |
| 3 | policy | | participants, healthcare professionals, the public, and other relevant |
| 4 | | | groups (eg, via publication, reporting in results databases, or other |
| 5 | | | data sharing arrangements), including any publication restrictions – |
| 6 | | | Pg 25 |
| 7 | | | |
| 8 | | 31b | Authorship eligibility guidelines and any intended use of professional |
| 9 | | | writers – 32-33 |
| 10 | | | |
| 11 | | 31c | Plans, if any, for granting public access to the full protocol, participant- |
| 12 | | | level dataset, and statistical code -- NA |
| 13 | | | |
| 14 | | | |

15
16 **Appendices**

| | | | |
|----|------------------|----|--|
| 17 | Informed consent | 32 | Model consent form and other related documentation given to |
| 18 | materials | | participants and authorised surrogates – Supplementary file |
| 19 | | | |
| 20 | Biological | 33 | Plans for collection, laboratory evaluation, and storage of biological |
| 21 | specimens | | specimens for genetic or molecular analysis in the current trial and for |
| 22 | | | future use in ancillary studies, if applicable - NA |
| 23 | | | |
| 24 | | | |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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